Immunosuppressives and Other Drugs

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Drugs that suppress the immune system are given to organ transplant patients to prevent the body from rejecting the donor organ. More recently, these drugs have also been used to treat a variety of autoimmune diseases, including severe rheumatoid arthritis. Azathioprine, adrenal corticosteroid hormones, and cyclosporin A are the most widely used immunosuppressive drugs, although other drugs, particularly many of the anticancer drugs, have immunosuppressive side effects in addition to the effects for which they are used.

Among transplant recipients treated aggressively with immunosuppressants, the risk of non-Hodgkin's lymphoma is increased to 50-fold or greater (Kinlen, 1992). These lymphomas often arise rapidly—within a year or two—after the transplant operation. They often develop in the brain, an unusual site for this type of cancer (Hoover, 1977). Some other cancers—skin cancers, soft-tissue (including Kaposi's sarcoma), as well as malignant melanoma, also occur at a higher rate in transplant recipients, although not nearly at the magnitude seen for the lymphomas.

Patients treated with these drugs for autoimmune diseases—generally at much lower doses—have about a ten-fold increased risk of lymphoma, adding to the evidence, from a number of sources, that the risk of this tumor is directly related to the intensity of the immunosuppressive treatment.

Other Drugs

Radioactive drugs contain a molecule "tagged" with a radioactive isotope; that isotope can be counted or imaged in diagnostic tests. Radioactive drugs can concentrate in body tissues and, depending on their strength and half-life, may injure those tissues. Radioactive drugs have also been used to treat tuberculosis of the bone, thyroid cancer, and the blood disorder polycythemia vera. Some of these radioactive drugs have been shown to cause various cancers, including osteogenic sarcoma, a type of bone cancer; leukemia; and a rare form of liver cancer (Hoover and Fraumeni, 1981).

In 1964, chlornaphazine, a drug used to treat polycythemia vera and Hodgkin's lymphoma, was withdrawn from the market because it was found to cause bladder cancer. Chlornaphazine is chemically related to beta-naphthylamine, a chemical earlier associated with bladder cancer among workers in the dye industry. Drugs containing inorganic arsenicals (e.g., Fowler's solution) are also no longer in clinical use. However, studies have shown that they can cause skin cancer. These cancers are typically multiple, involve unexposed parts of the body and unusual locations, and are associated with arsenical pigmentation and hyperkeratosis.

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Other drugs have also been found to increase the rate of human cancers. Pain-killing drugs that contain phenacetin have been linked to kidney cancers, and a photochemotherapy regimen for psoriasis which combines methoxysporalens with ultraviolet-A exposure (PUVA) has been linked with skin cancer.

For a number of other medications there is some evidence of a cancer hazard, but conflicting studies or other inconsistencies in the evidence make them merely suspect. For two such categories of drugs, coal tar ointments and thiazide diuretics, the accumulating evidence is particularly worrisome. Coal tar ointments contain known carcinogenic chemicals (polycyclic hydrocarbons), and the relationship of use of these ointments to risk of skin cancer has been a matter of debate for some time. The evidence from studies of psoriasis patients treated with high doses over protracted periods at this time seems to indicate an excess risk. The data concerning a possible relationship between use of thiazide diuretics and excess risk of kidney cancer illustrate one of the problems in interpreting any drug-cancer association, that is, the ability to separate a drug effect from an effect of the condition for which the drug is prescribed. There have now been more than ten studies, of various designs, which have identified an excess risk of kidney cancer among users of thiazide diuretics. To date, it has not been possible to disentangle the effect of the drug from a potential effect of high blood pressure—the reason the drug was prescribed in the vast majority of patients in these studies. With the high prevalence of use of this medication, clarifying these relationships should have a high priority.

There are occasional suggestions that some medications may actually be associated with a reduced risk of cancer. Perhaps most provocative of these has been the recent observation that frequent users of aspirin or other nonsteroidal anti-inflammatory drugs experience fewer cancers of the colon than expected (Thun, 1991).

It may even be that some medications will be found to be protective against some cancers while causing others. This seems to be the emerging pattern associated with the use of tamoxifen. Women taking this drug as part of a treatment regimen for breast cancer experience a substantially reduced incidence of a second primary breast cancer compared to breast cancer patients who don't receive the drug. Conversely, the drug appears to be associated with an increased risk of cancers of the lining of the uterus (endometrium). This would be consistent with the differing hormonal effects this drug has in these two organs, since it acts as an estrogen in the uterus and as an antiestrogen in the breast (Nayfield et al., 1991; Fisher et al., 1994).

REFERENCES

Fisher B, Costantino JP, Redmond CK, et al.: Endometrial cancer in tamoxifen-treated breast cancer patients: Findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) b-14. *J Natl Cancer Inst* 86:527-537, 1994.

Hiatt RA, Tolan K and Quesenberry CP Jr: Renal cell carcinoma and thiazide use: a historical, case-control study. *Cancer Causes Control* 5:319-325, 1994.

Hoover R and Fraumeni JF Jr: Drug-induced cancer. *Cancer*, 47:1071-1080, 1981.

Hoover R: Effects of drugs: immunosuppression. (Hiatt, Watson, Winsten, eds.). In Origins of Human Cancer. Cold Spring Harbor Lab. Press 369-379, 1977.

Hoover RN: Cancer induced by cancer treatment. (Fortner, Rhoads, eds.). In Accomplishments in Cancer Research, 1992. Philadelphia: J.B. Lippincott, 1994, 229-239.

Kinlen LJ: Immunosuppressive therapy and acquired immunological disorders. *Cancer Res* [suppl] 52:5474s-5476s, 1992.

Nayfield S, Karp JE, Ford LG, et al.: Potential role of tamoxifen in prevention of breast cancer. *J Natl Cancer Inst* 83:1450-1459, 1991.

Thun MJ, Namboodiri MM, Heath CW Jr: Aspirin use and reduced risk of fatal colon cancer. *N Engl J Med* 325(23):1593-1596, 1991.